Difficult to Treat Depression

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Old Ways

- Switching antidepressants
- High dose antidepressants
- Stimulant augmentation
- Aug with buspirone or antidepressants
- Antipsychotic augmentation*
- Rapid acting treatments*
- Impressionistic care

*These are effective short-term not long-term.
The others are ineffective.

New Ways

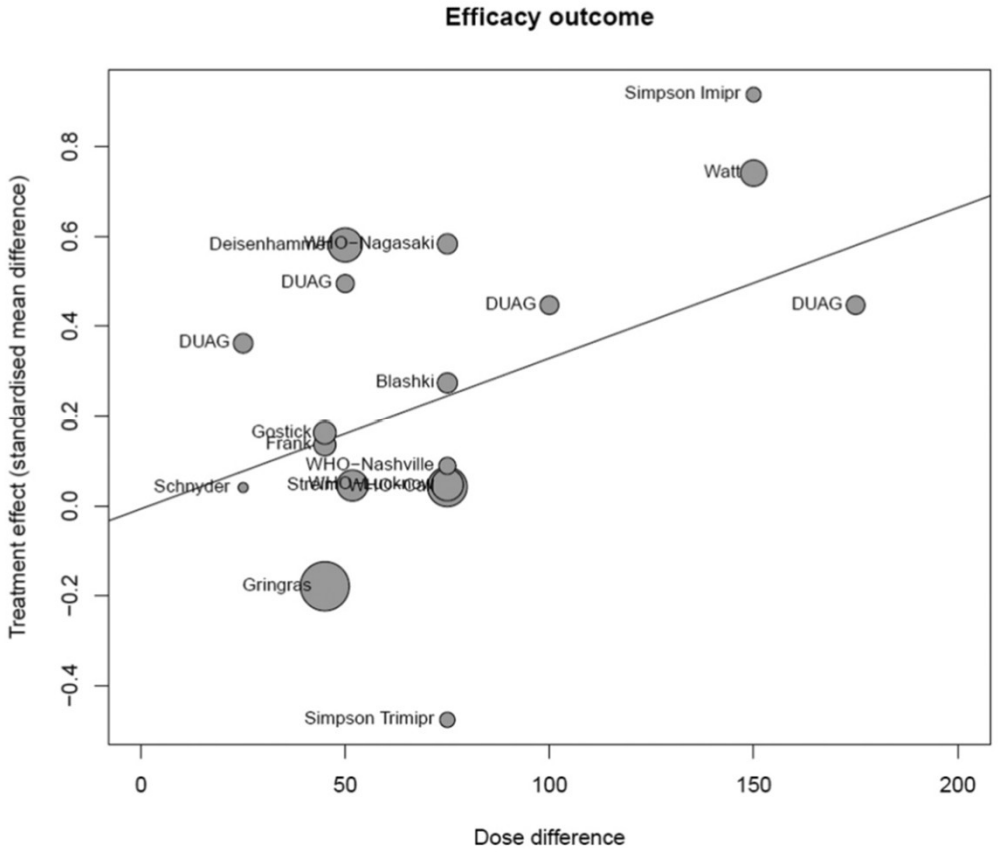
- Psychotherapy
- Personalize by subtypes
- Address deficits
- Aug with lithium or pramipexole
- Neuromodulation (SAINT TMS, ECT)
- Long lasting treatments
- Measurement-based care

Tricyclic Dose Response

Every increase of 100 mg imipramine equivalents =

0.34 effect size difference

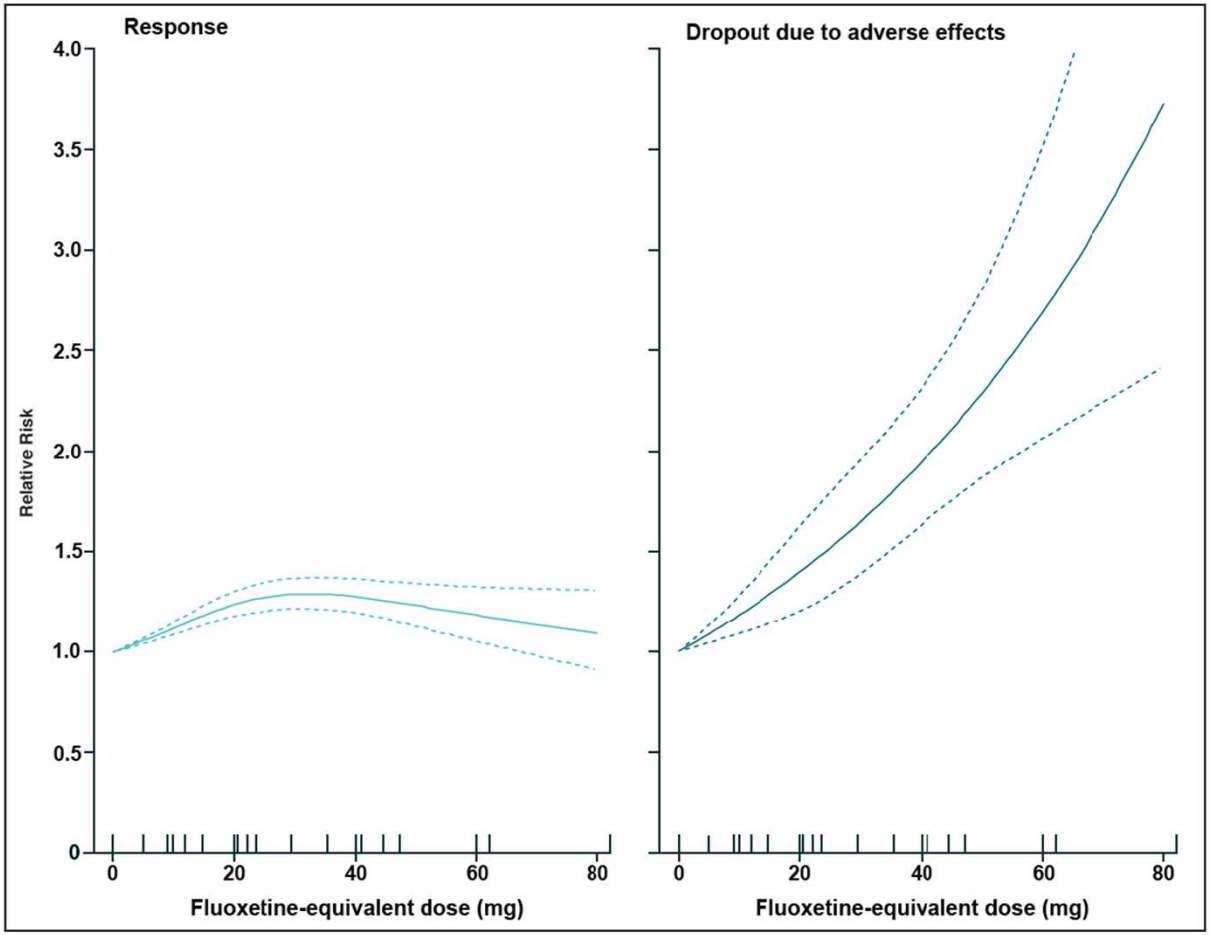
Imipramine 100 mg =
Amitriptyline, desipramine, doxepine 100 mg =
Amoxapine 167 mg =
Clomipramine, maprotiline 83 mg =
Nortriptyline 74 mg =
Protriptyline 19 mg =
Trimipramine 85 mg



15 RCTs of fixed dose comparisons. Baethge C et al. J Affect Disord. 2022;307:191-198.

SSRI Dose-Response

Peak benefits at 20-40 mg fluoxetine equivents



99 fixed-dose groups. Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609.

Antidepressant Dose-Response

Dose-response:
Tricyclics
Reboxetine
Venlafaxine (to 225 mg)
Desvenlafaxine (to 200 mg)

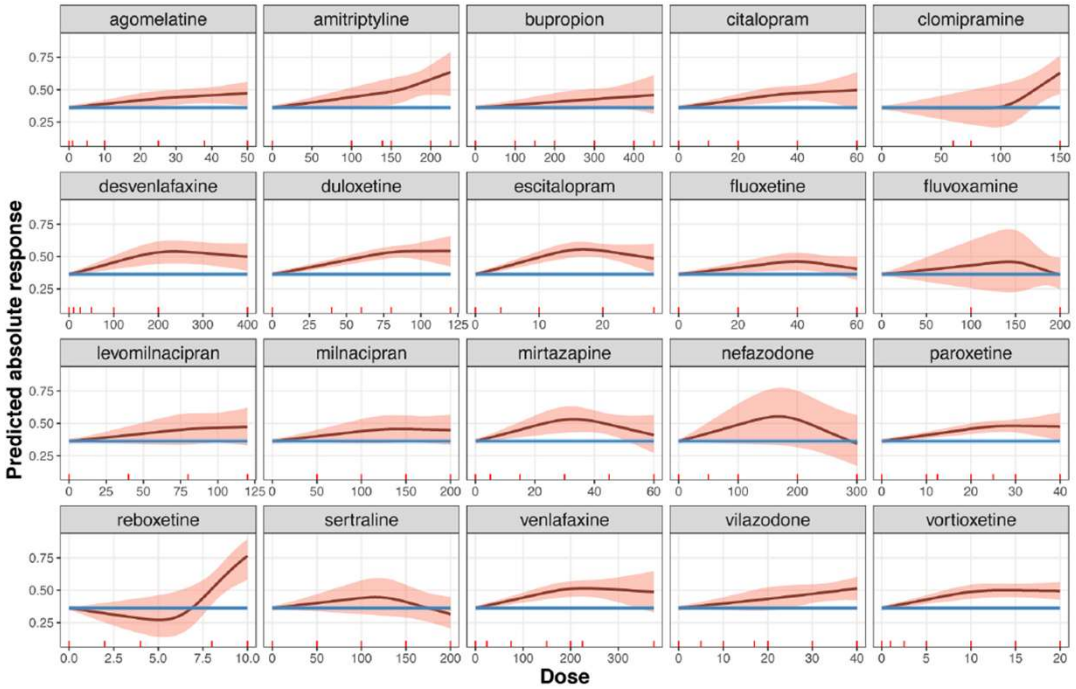


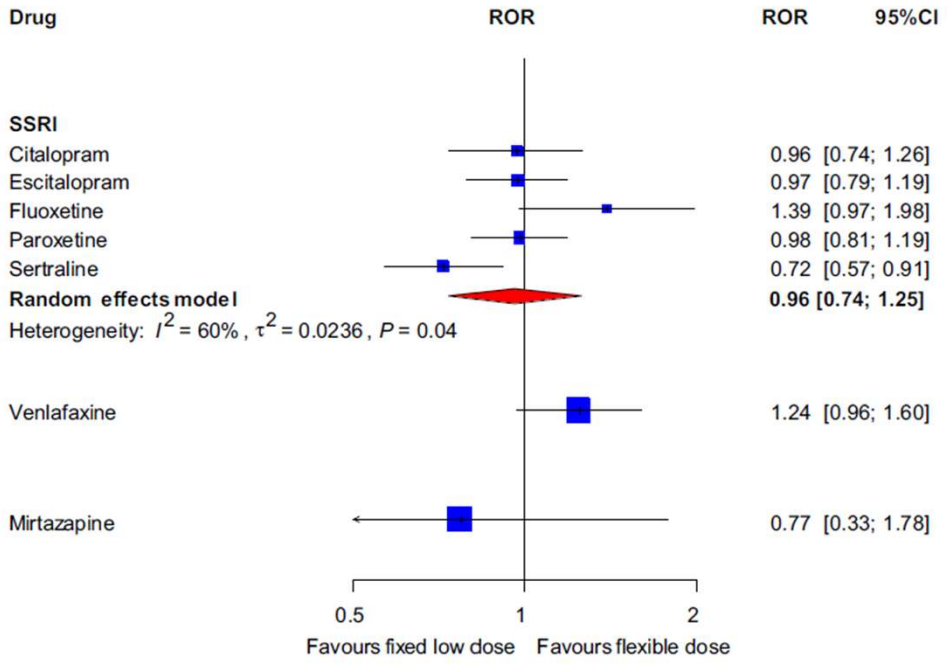
Figure 2. Dose–effect network meta-analysis summary curve for each antidepressant. The blue line depicts the effect estimated from all placebo arms in the network (36.2%) with its 95% credible region. The red line represents the absolute response to each antidepressant (estimated from model M1) and the shaded area is its 95% credible region.

Network metaanalysis of 120 trials. Hamza T et al, Stat Methods Med Res, 2/2022.

Raise the dose vs. give it more time?

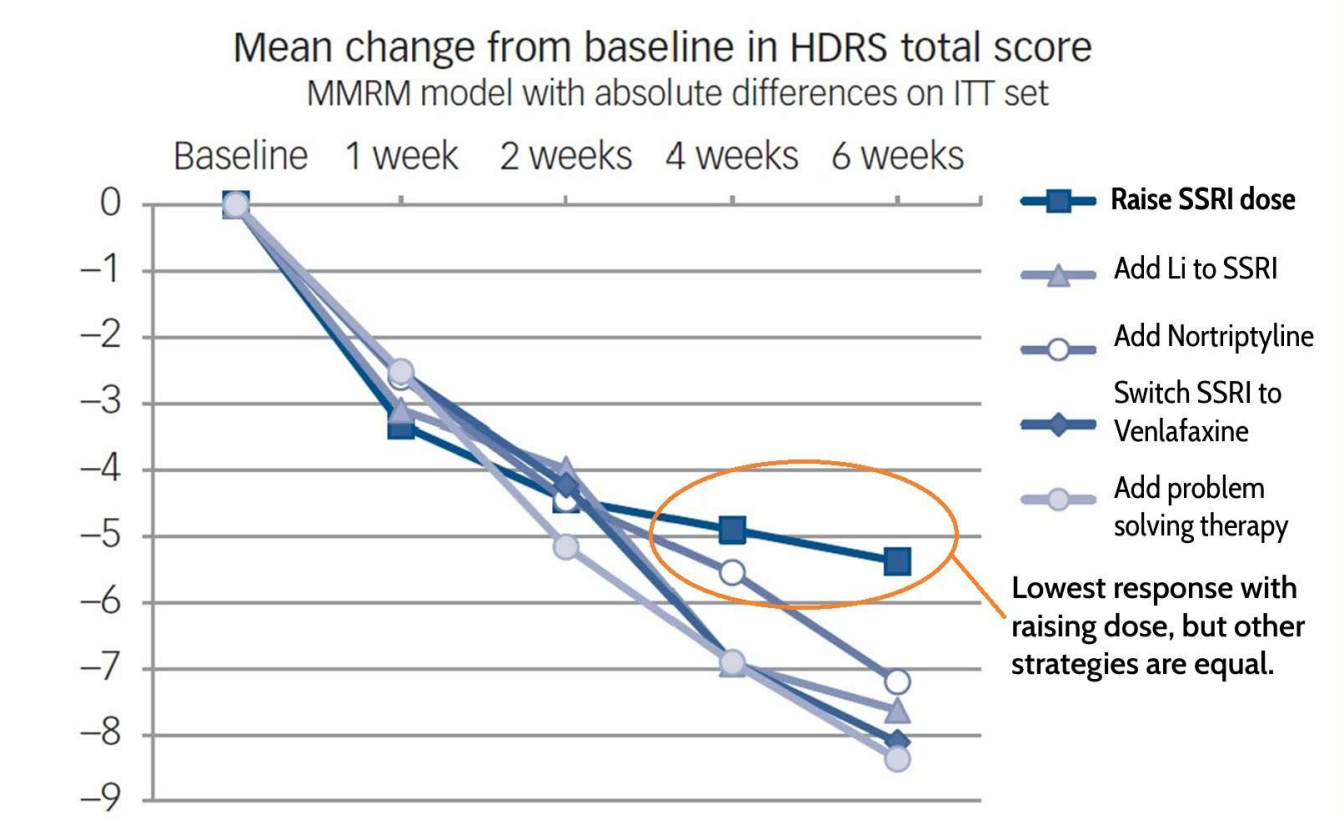
No benefit: Raising SSRIs or mirtazapine.

Yes benefit: Raising venlafaxine 75 → 150 mg.



Metaanalysis of 123 trials. Furukawa TA et al, Acta Psychiatr Scand. 2020;141(5):401-409.

Raising Dose = Least Effective Strategy



Pérez V et al, Br J Psychiatry. 2025 Jun 18:1-8

Stimulant Augmentation

No benefit:

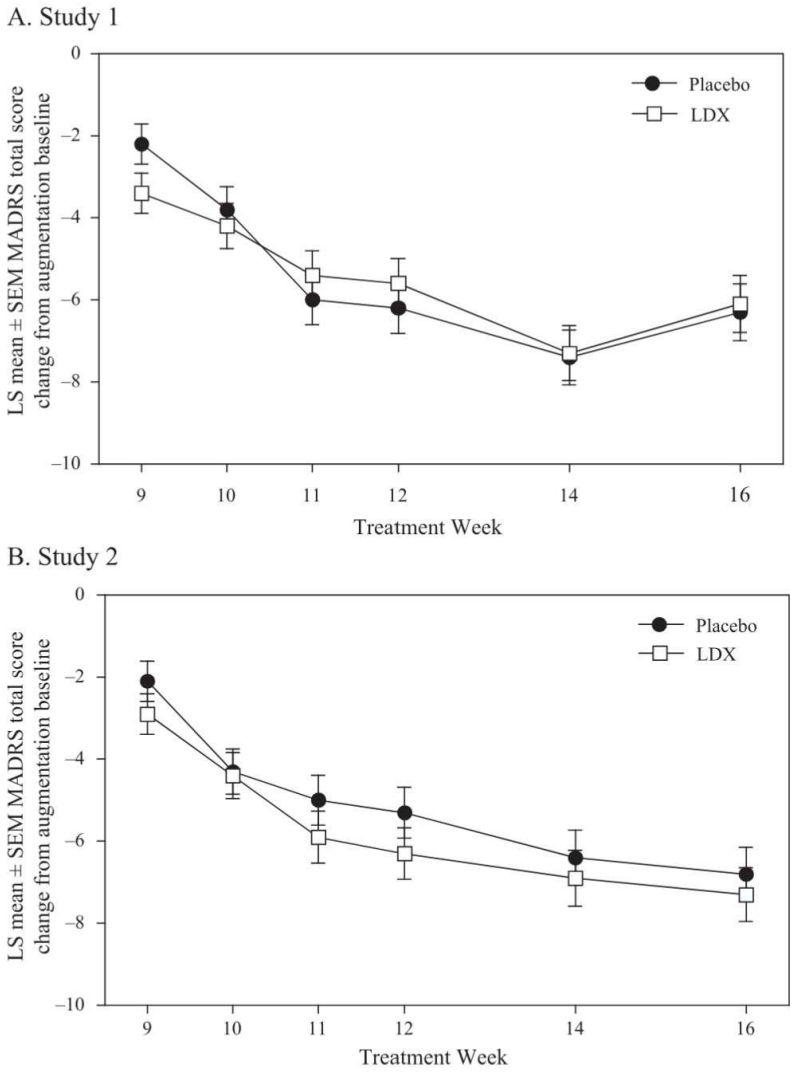
Lisdexamfetamine (3 RCTs n=1,218)

Methylphenidate ER (2 RCTs n=205)

Other augmentation failures:

Bupropion, mirtazapine, buspirone, thyroid T3 (in large RCTs/meta-analyses)

Richards C, et al. J Affect Disord 2016;206:151-160.
Ravindran AV et al, J Clin Psychiatry. 2008;69(1):87-94.
Patkar AA et al, J Clin Psychopharmacol. 2006;26(6):653-656.
Trivedi MH et al, J Clin Psychiatry. 2013;74(8):802-809.



Personalize by Subtype

What Type of Depression?

Bipolar depression (30-40%)

Unipolar with mixed features (25%)

Psychotic depression (20%)

Vascular depression (50% after age 65)

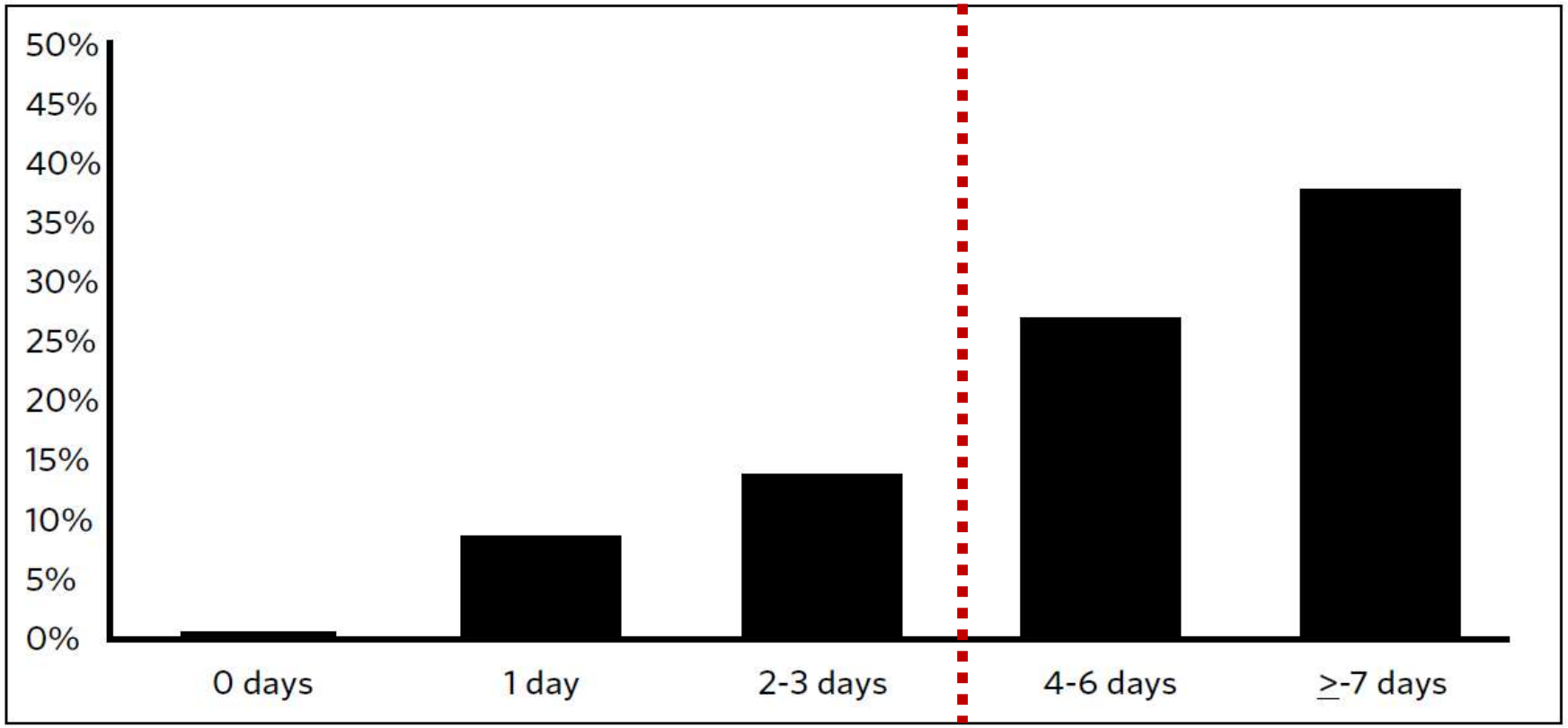
Inflammatory depression (30%)

These rates ~30% higher in TRD

Bipolar Disorders			Non-bipolar Depression		
Bipolar I	Bipolar II	Cyclo-thymic	Brief hypomania	Mixed features	Pure depression (no hypo/mania)

Manic-depressive illness (pre-DSM III)

Neurotic traits
Chronic stress
Early trauma
Other causes



Risk of (h)mania on antidepressant rises with duration of past (h)manic symptoms

Angst J et al, *Eur Arch Psychiatry Clin Neurosci*, 2012, 262(1), 3-11.

Psychotic Depression

30% of cases are missed

ECT is gold-standard (>90% remission)

Antipsychotic augmentation is intuitive but weak (d=0.25) and requires schizophrenia-level dosage

Lithium augmentation (uncontrolled trials)

Rothschild AJ et al, J Clin Psychiatry 2008;69(8):1293–1296; Petrides G et al, J ECT. 2001;17(4):244-253; Farahani A and Correll CU, J Clin Psychiatry 2012;73(4):486–496; Birkenhäger TK et al, J Clin Psychopharmacol 2009, 29(5):513-515; Ebert D, J Clin Psychopharmacol 1997;17(2):129-130

Inflammation

- Childhood trauma
- Mixed features, Anhedonia
- Chronic medical illness
- Obesity (BMI ≥ 30), Western diet
- Smoking, sedentary lifestyle
- Recent chemotherapy or radiation
- Recent bodily injury or surgery
- Recent infection
- Postpartum, Menopause, Older age
- Elevated C-Reactive Protein (hs-CRP) ≥ 3

Medication for Inflammatory Depression

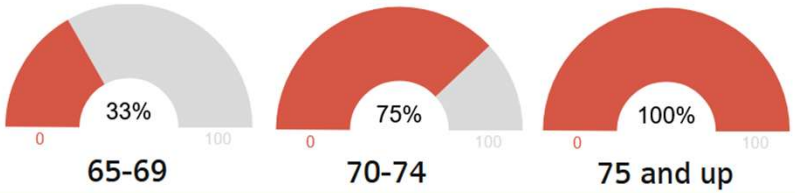
	Rationale
Bupropion	↑CRP and obesity predicts response to augmentation
Celecoxib	↑CRP predicts response. Anti-inflammatory with 17 randomized trials in depression (200 mg BID).
Pramipexole	Targets the dopamine tracks that are disrupted by inflammation. Reduced inflammatory markers and anhedonia in trials of depression (0.5-2.5 mg QHS)
? Lithium	Anti-inflammatory mechanisms
Nortriptyline	↑CRP predicts response (versus SSRI)
Minocycline	Anti-inflammatory properties. Results mixed in depression, but trend positive with ↑CRP (100 mg BID).

Naturals for Inflammatory Depression

	Rationale
Omega-3	↑CRP predicts response, esp to higher dose (4,000 mg/day, EPA:DHA ≥ 2:1)
N-Acetylcysteine (NAC)	↑CRP predicts response
L-Methylfolate	↑CRP predicts response in unipolar; positive trials in bipolar
Lifestyle	Exercise, Mediterranean diet, CBT-insomnia, stress reduction

Mischoulon D et al, J Clin Psychiatry 2022;83(5):21m14074
Shelton RC et al, J Clin Psychiatry 2015;76(12):1635–1641
Porcu M et al, Psychiatry Res 2018;263:268–274

Vascular Depression



- Cardiovascular risk factors
- MRI white matter hyperintensities
- Cognitive deficits
- Psychomotor retardation, lack of insight
- More responsive to TMS or nimodipine (start 15-30 mg TID, target 90 mg TID)

Taylor WD et al, *Am J Psychiatry* 2018;175(12):1169-1175
Park JH et al, J Affect Disord 2015;180:200-206
Taragano FE et al, Int J Geriatr Psychiatry 2001;16(3):254–260
Taragano FE et al, Int Psychogeriatr 2005;17(3):487–498

Address Deficits

Treatments that address deficits in depression

- Light therapy
- Methylfolate
- Vitamin D
- Omega-3 fatty acids
- Probiotics

Methylfolate effect size = 0.4-0.9*

Risks

None

Tolerability

None

Cost

15 mg/day, $7.50/month

Recommended Products:

chrisaikenmd.com/supplements

*0.9 in large RCT of depression with MTHFR genotype abnormalities, as monotherapy in vitamin-complex Enlyte:

Mech AW and Farah A, J Clin Psychiatry 2016;77(5):668-71

0.4 in metaanalysis of depression augmentation trials:

Maruf AA et al, Pharmacopsychiatry 2022;55(3):139-147

Light Therapy effect size = 0.5-0.8*

Risks

Photosensitivity. Caution in eye disease.

Tolerability

Headache, eye strain.

Cost

$120-200 (one time)

Recommended Products:

chrisaikenmd.com/lighttherapy

*0.5 in non-seasonal depression, 0.5-0.8 in winter seasonal depression, 0.4 in bipolar depression

Mårtensson B et al, J Affect Disord 2015;182:1-7
Tao L et al, Psychiatry Res 2020, 291:113247
Lam RW et al, Can J Psychiatry 2020;65(5):290-300

Antipsychotic effect size = 0.3-0.4

Risks

Tardive dyskinesia

Metabolic syndrome

Hyperprolactinemia

Orthostatic hypotension

Arrhythmias

Hyperthermia

Neuroleptic Malignant Syndrome

Priapism

Neutropenia

Elevated LFTs

Mortality in dementia

Tolerability

Akathisia

Dystonia

Muscle stiffness (EPS)

Weight gain

Sedation

Sexual dysfunction

Anticholinergic effects

Think Longterm

Rapid acting treatments

Benzodiazepines (alprazolam)

Eszopiclone

Pindolol

Bupropion-Dextromethorphan (Auvelity)

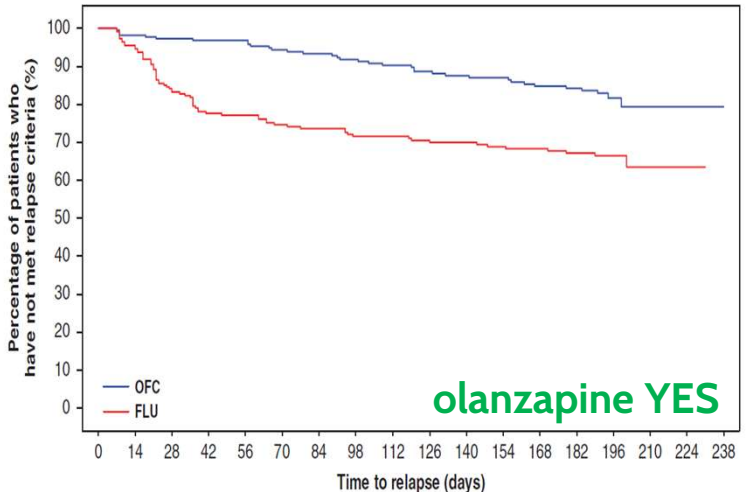
Ketamine and Esketamine

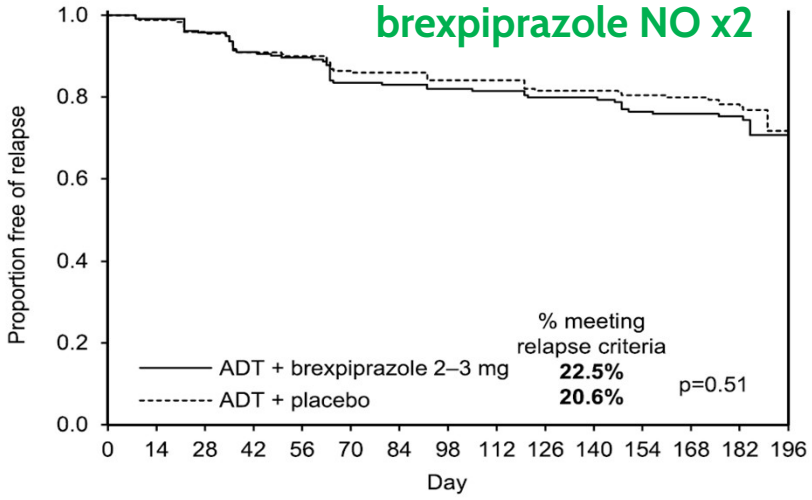
Zuranolone (for postpartum)

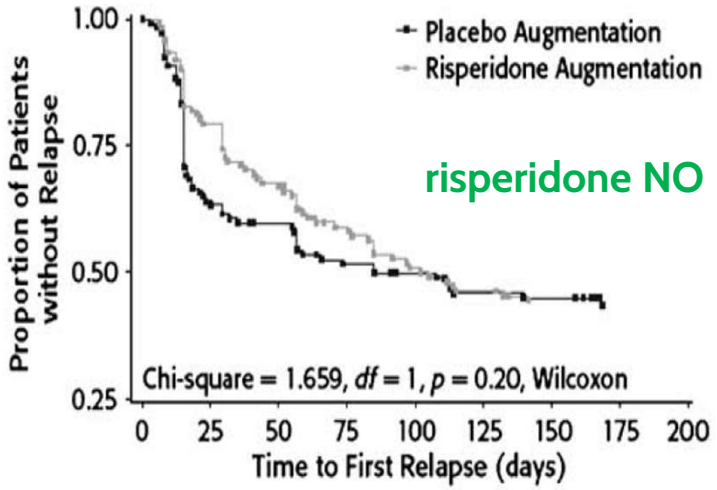
Psychedelics

Does antipsychotic continuation prevent depression?

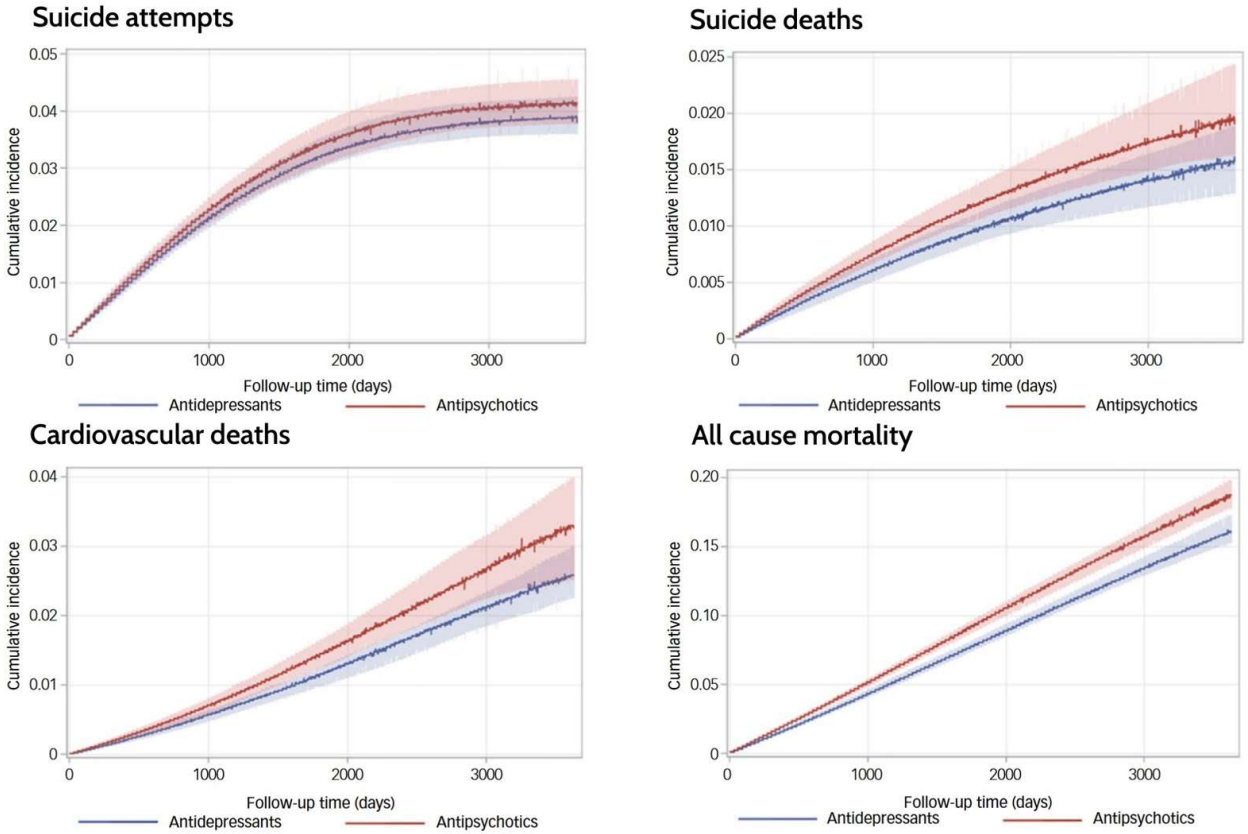
Not in 3/4 trials (6 months, n=2,308)







Antipsychotics don't prevent suicide, may raise mortality

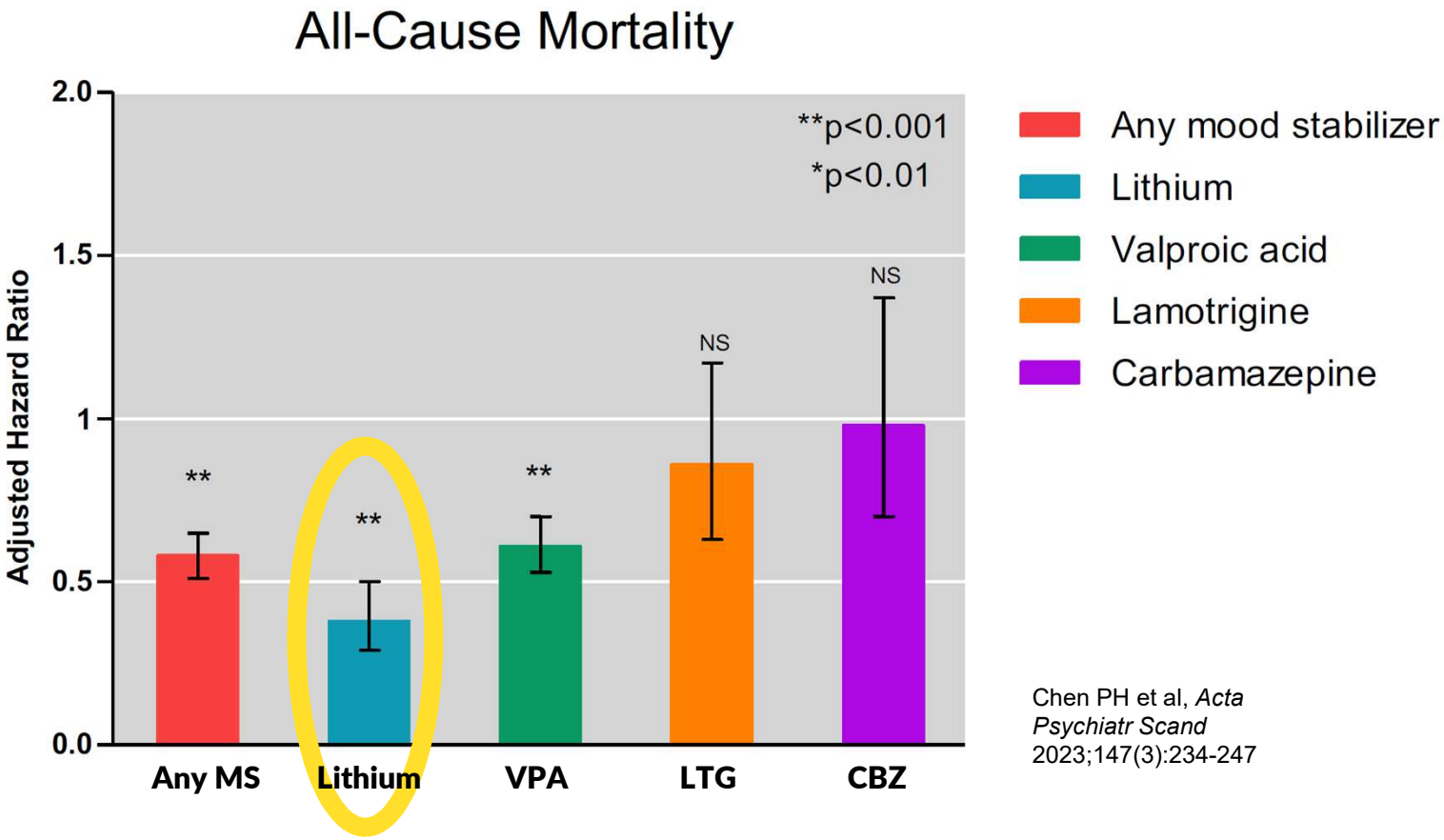


Comparative cohort study of 79,898 patients with TRD.

Antipsychotic augmentation vs. matched controls who received third-line antidepressants

Tsai DH et al, Brit J Psychiatry 2025;1-9

Lithium lowers medical and suicide mortality



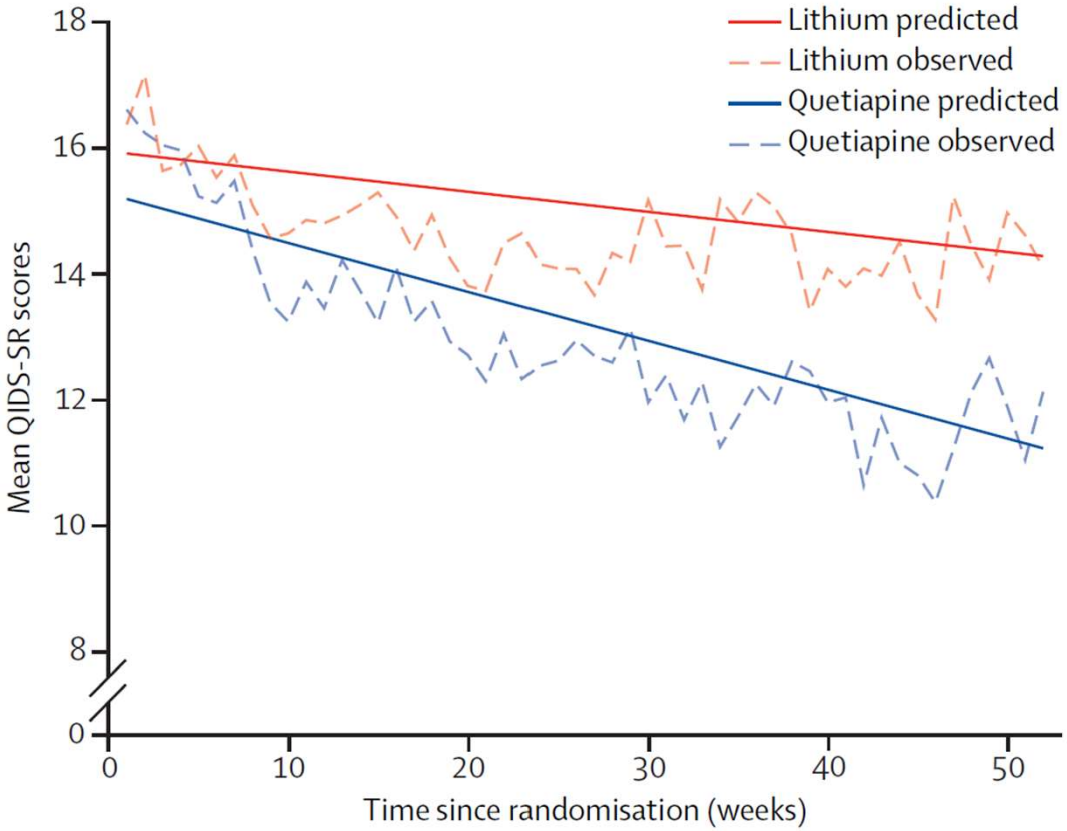
Chen PH et al, *Acta Psychiatr Scand* 2023;147(3):234-247

Lithium prevents unipolar depression

- 21 controlled trials, average duration 2 years
- Also prevents depression after ECT
- Prevents suicide and hospitalization more than antidepressants and antipsychotics in unipolar
- Acute benefits similar to antipsychotics (12 trials, NNT=5)

Undurraga J et al, J Psychopharmacol 2019;33(2):167-176
Lambrichts S et al, Acta Psychiatr Scand 2021;143(4):294-306
Tiihonen J et al, Lancet Psychiatry. 2017;4(7):547-553
Pompili M et al, J Affect Disord 2023, 340:245-249

Quetipine vs Lithium Aug in TRD



Randomized controlled trial

- One year
- n = 212, 60% failed ≥ 3 antidepressants
- Lithium mean 0.85, quetiapine 195 mg

Pérez V et al, Br J Psychiatry. 2025 Jun 18:1-8

Lithium

Start 150-300 mg hs
Raise every 3-5 days to 600-900 mg
Target level 0.6-0.8
(aim ~30% lower if age 65+)

Labs every 3-12 months
Li, electrolytes (Ca, Cr, eGFR), TSH
Check parathyroid if ↑Ca

Preferential response in recurrent depression, suicidality, elderly, post-ECT

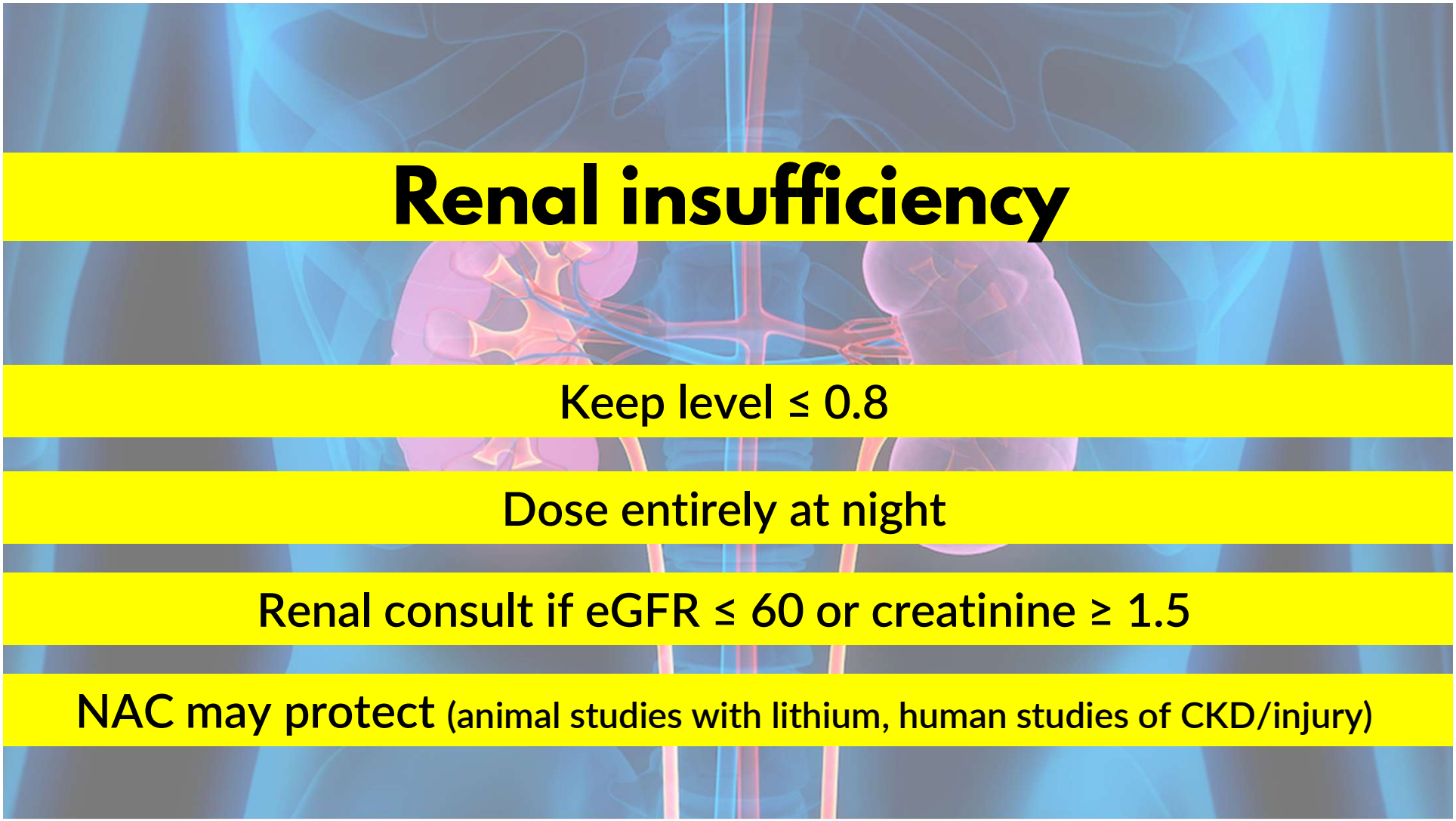
Tolerability

Nausea, tremor
Low weight gain and sedation (1:28)

Risks

Renal insufficiency, hypothyroidism (15%), hyperparathyroidism (4%), SIADH, psoriasis, cardiac (bundle branch block), drug interactions, toxicity

Lambrichts S et al, Acta Psychiatr Scand 2021;143(4):294-306; Buspavanich P et al, J Affect Disord. 2019;251:136-140; Christl J et al, 2023;56(5):e1



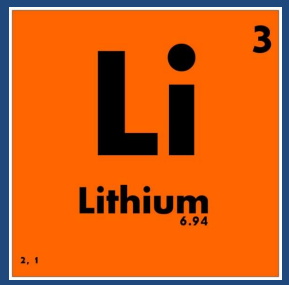
Renal insufficiency

Keep level ≤ 0.8

Dose entirely at night

Renal consult if eGFR ≤ 60 or creatinine ≥ 1.5

NAC may protect (animal studies with lithium, human studies of CKD/injury)



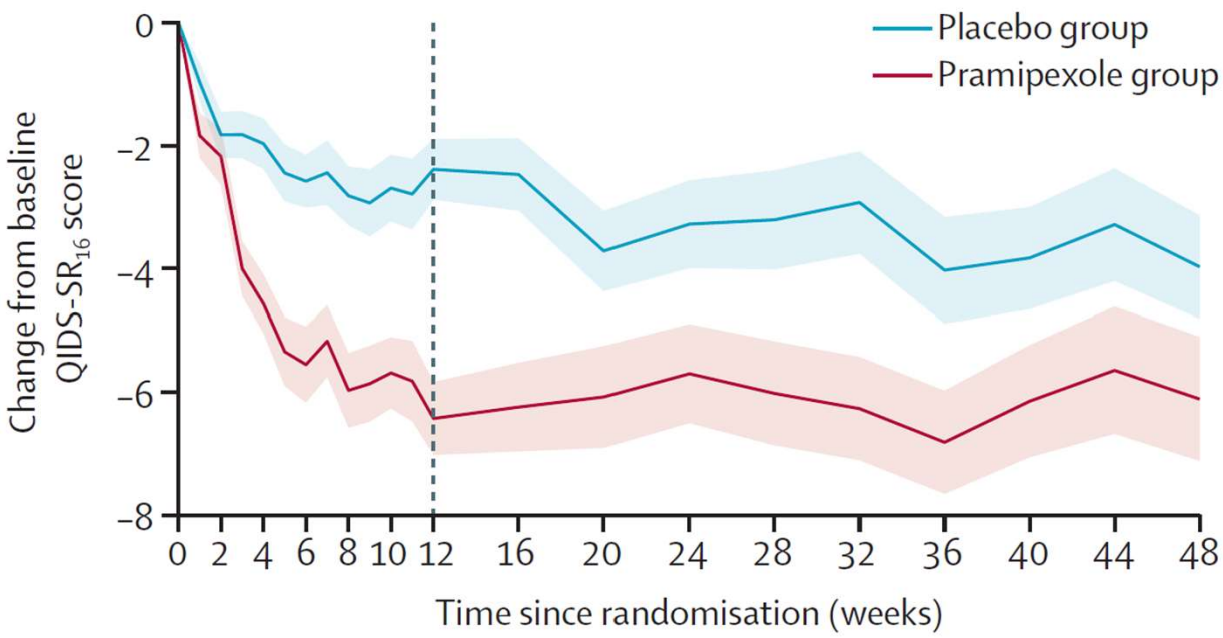
Side Effect Guide

Antidote	Use	Potential Psych Benefits	Dose (mg/day)
Propranolol	Tremor	Anxiety. AP-akathisia.	80-240
Vitamin B6*	Tremor	Depression. AP-akathisia, EPS, prolactinemia, TD.	500-1,000 divide BID-TID
Nimodipine	Tremor	Ultra-rapid cycling	240-480 divide TID
Gabapentin	Tremor	Social anxiety, alcohol, cannabis	600-1200 divide BID-TID
Ondansetron	Nausea	OCD, binge drinking, bulimia	4 mg q12 hr
Ginger	Nausea	Cognitive decline	1,000-2,000 mg q12hr
Amiloride	Nephro. Diabetes Insipid.	n/a	5
Aspirin	Sex dys in men	n/a	240
Minocycline	Acne	Depression	100-200
Probiotics	Acne	Depression, anxiety	Take with fiber
Omega-3	Acne, psoriasis	Depression	2000-3600 of EPA + DHA
Inositol	Psoriasis	Depression, bulimia	12,000-18,000
NAC*	Renal protect	Depression, cannabis	1,200-2,000

*Risk of neuropathy may be avoided by using active form, pyridoxal 5′-phosphate, at 50-70% lower dose

*NAC (N-acetylcystine) has animal studies for lithium-renal toxicity, human trials in renal failure and bipolar depression

Pramipexole Augmentation in TRD



Randomized, placebo controlled trial:

- 48 weeks
- n = 150, avg 3.5 trials; 21% tried augmentation
- 2.3 mg qhs (mean)
- Effect size 0.9

Browning M et al, Lancet Psychiatry, June 29, 2025.

Pramipexole

Target 1-3 mg hs (average 1.5)

Start 0.125-0.25 mg,
raise by 0.125-0.25mg q3-7 days,
raise faster after 0.75 mg

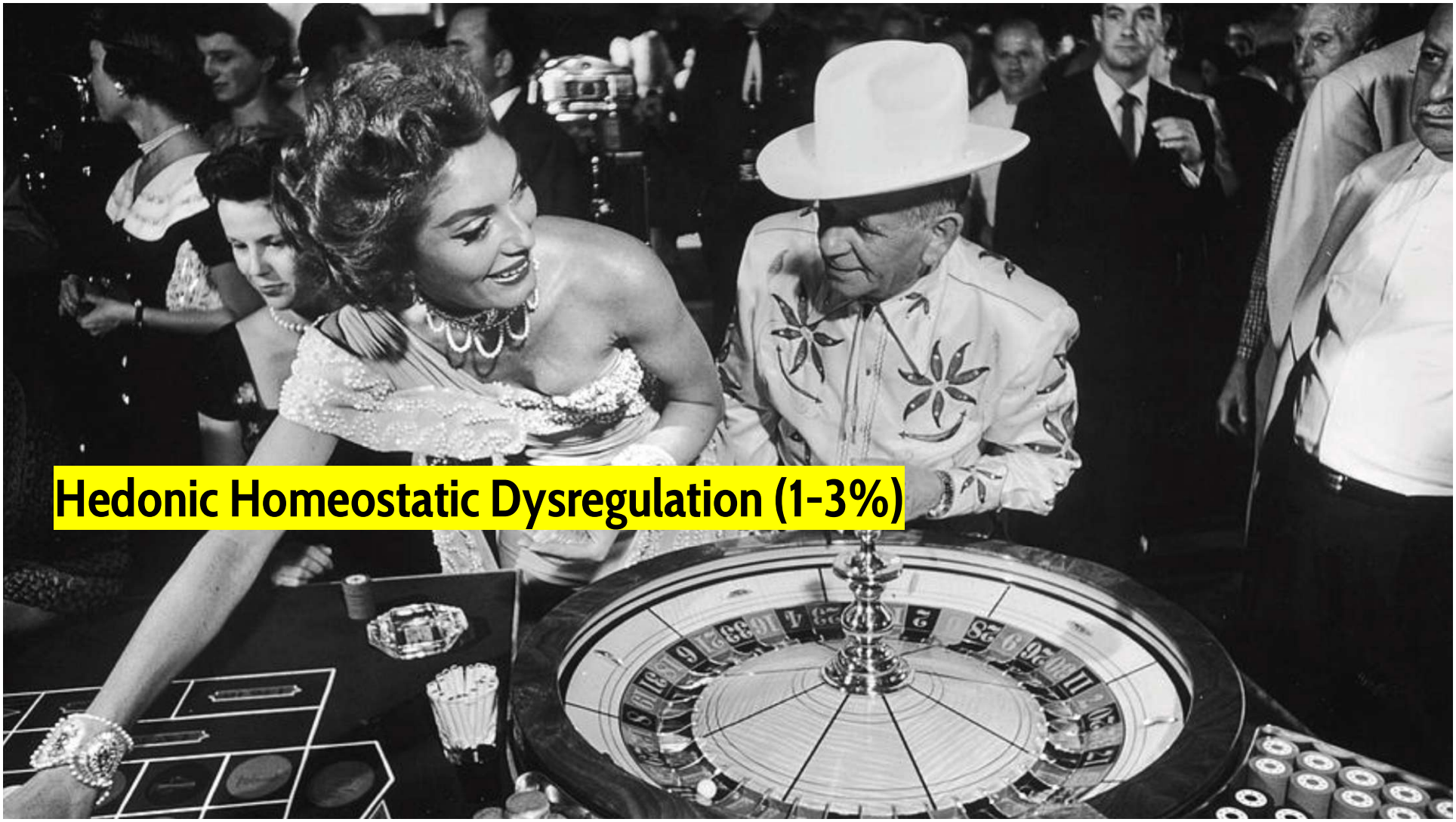
Large effect in RCTs of unipolar (4) and bipolar (2) depression

Prefer for anhedonia, inflammation, bipolar spectrum, comorbid restless leg syndrome

Tolerability
Nausea, sedation.
No weight/sexual/cognitive

Risks
Hedonistic dysregulation (approx. 1-3%)
Hallucinations (rare at dose < 2 mg)
Hypotension

Dopamine D3 receptors in the nucleus accumbens regulate hedonic drive


Hedonic Homeostatic Dysregulation (1-3%)


Compulsive masturbation at work
Cleaning garage
Excessive videogames
Sorting bookshelves alphabetically

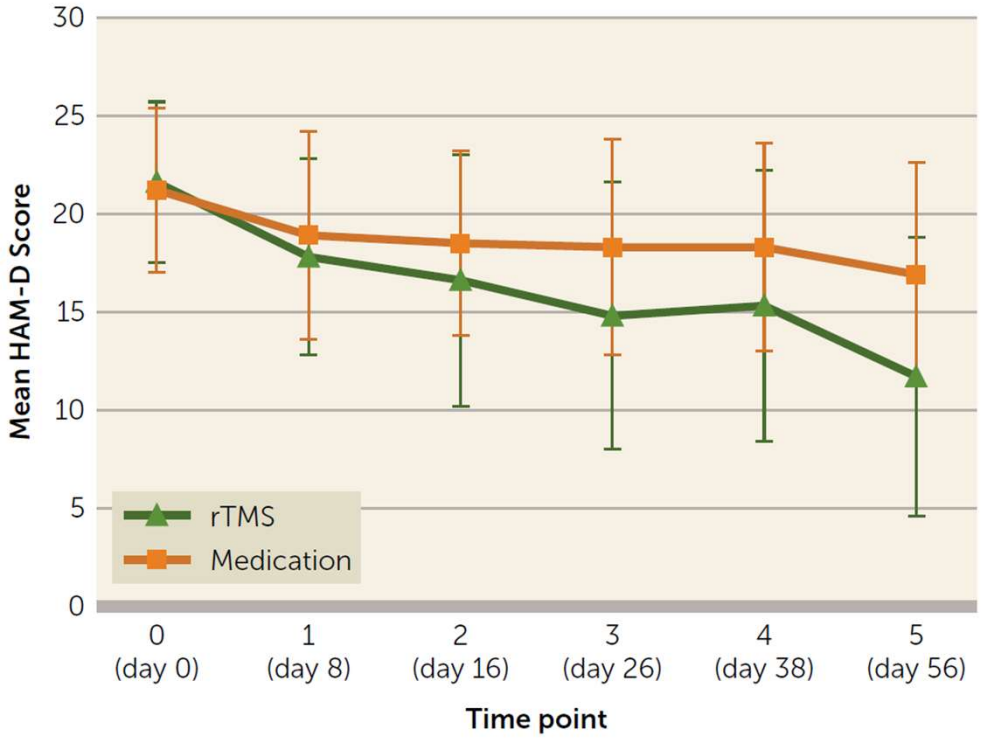
Neuromodulation

"by this method we eliminate the pain for the moment being and cure evil pain in the future“

–Scribonius Largos (1st century AD)

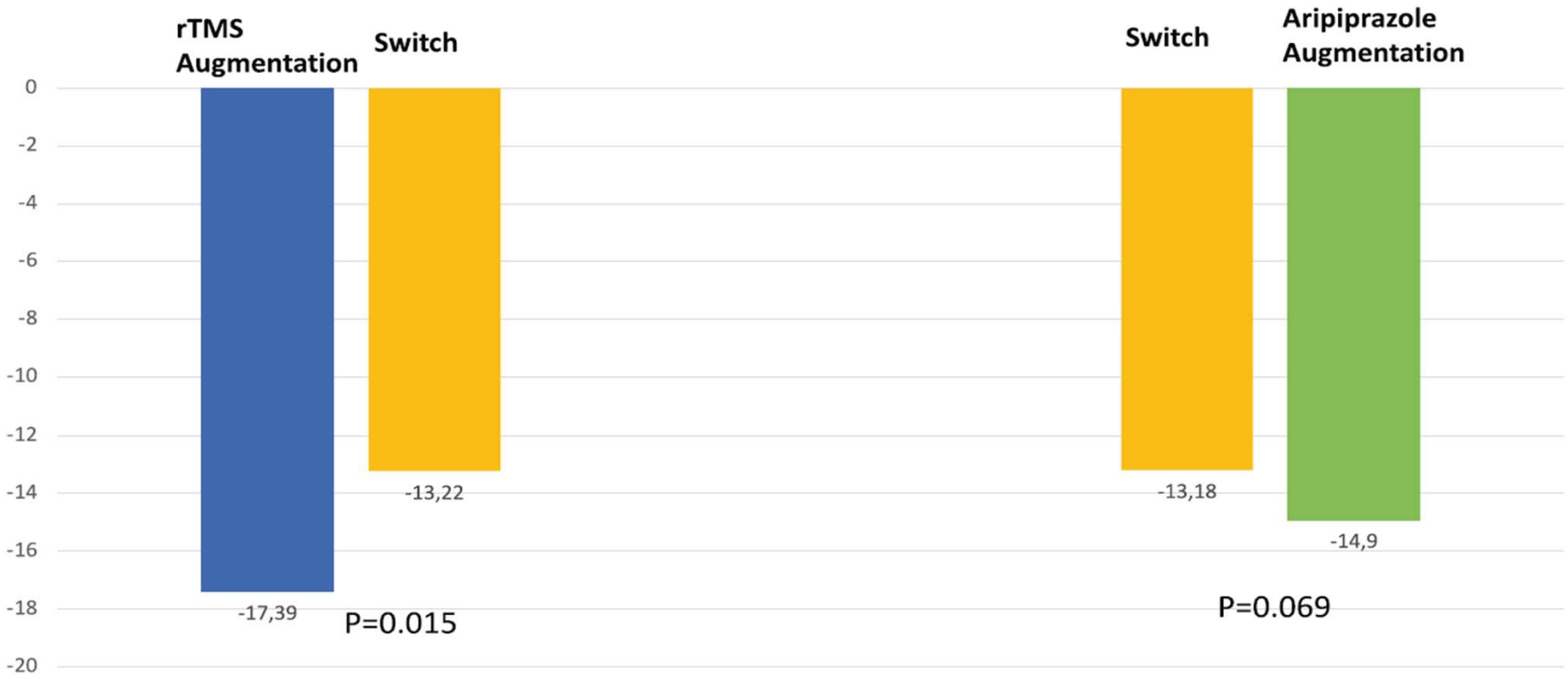
rTMS vs tricyclic switch in TRD

FIGURE 2. Depression severity over time with repetitive transcranial magnetic stimulation (rTMS) or a switch in antidepressant medication[a]



Dalhuisen I et al, Am J Psychiatry. 2024;181(9):806-814.

TMS More Effective than Aripiprazole Aug in TRD



8 week RCT n = 278, meand dose 9 mg

Papakostas GI et al, Mol Psychiatry. March 7, 2024.

SAINT TMS

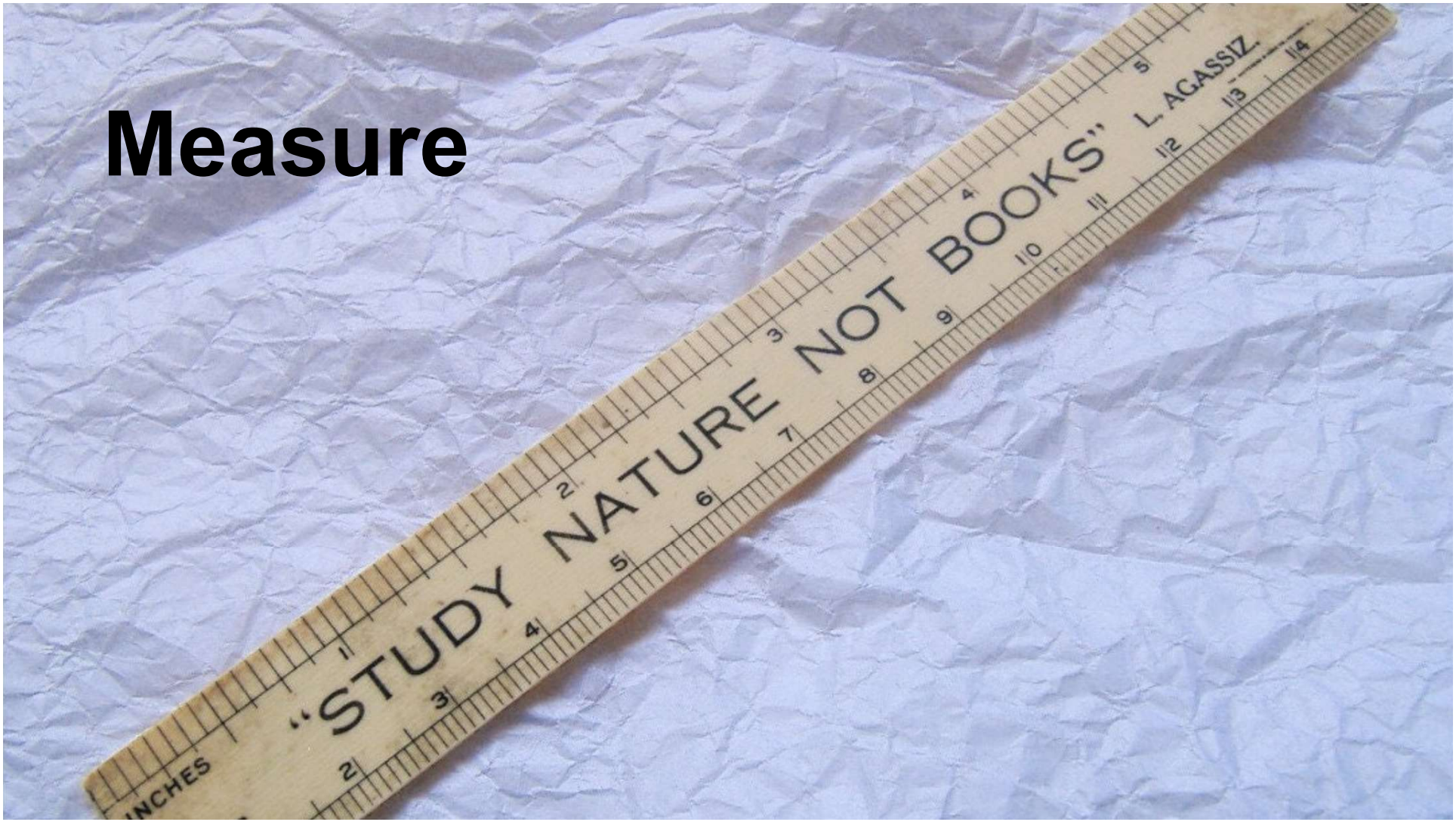
- Five day course...
- Ten hours a day...
- One 3-minute iTBS per hour

- fMRI guided magnet placement

- Remission 79% (vs 13% sham)
- Maintained at one year with PRN treatment (approx. 1 day/month)

Cole EJ et al, Am J Psychiatry 2022;179:132–41
Stimpson K et al, Brain Stimul 2025, 18:208e617

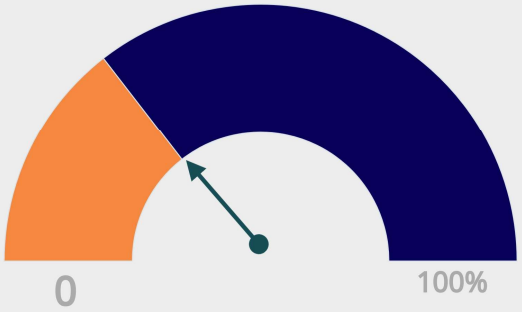
Measure



Regular Measurement Raises Remission in Depression

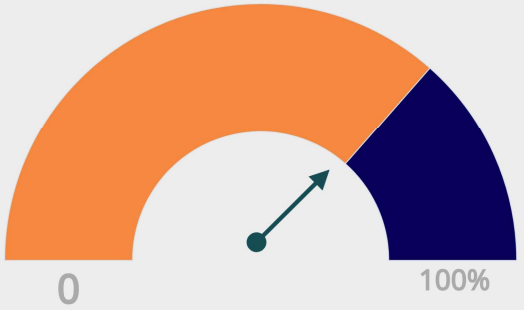
Usual Care

29%



Measurement-Based Care*

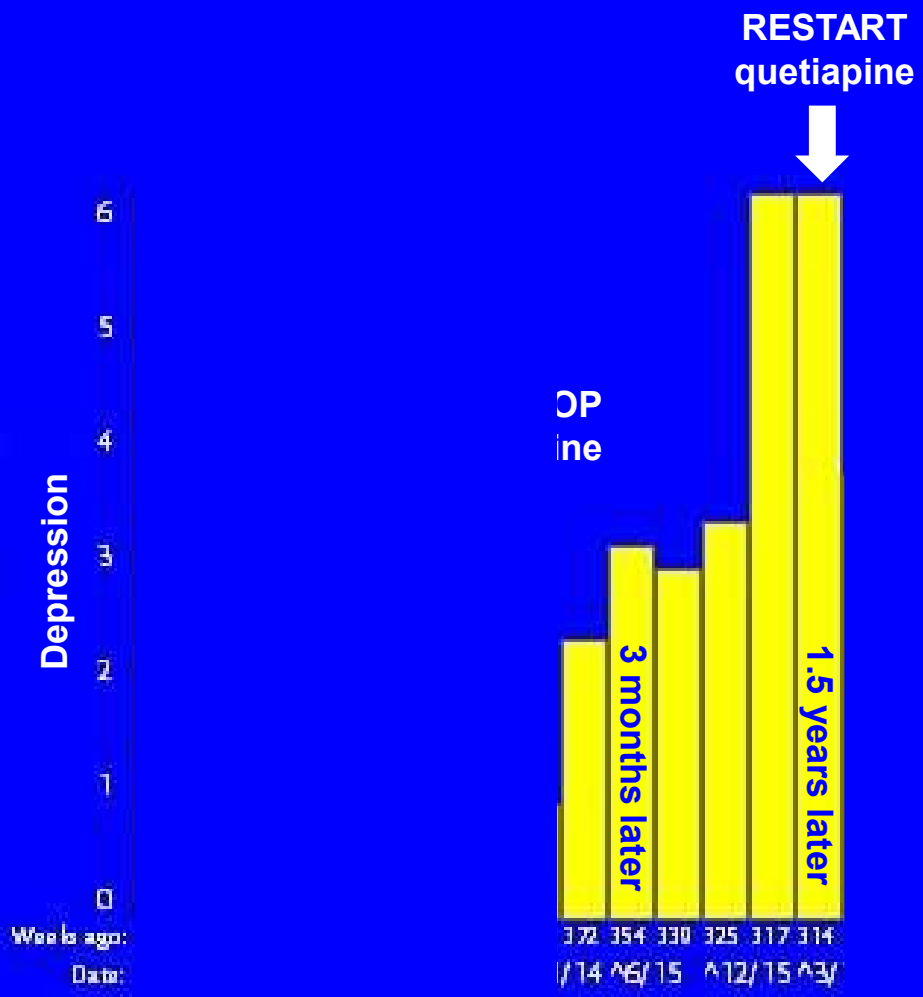
73%



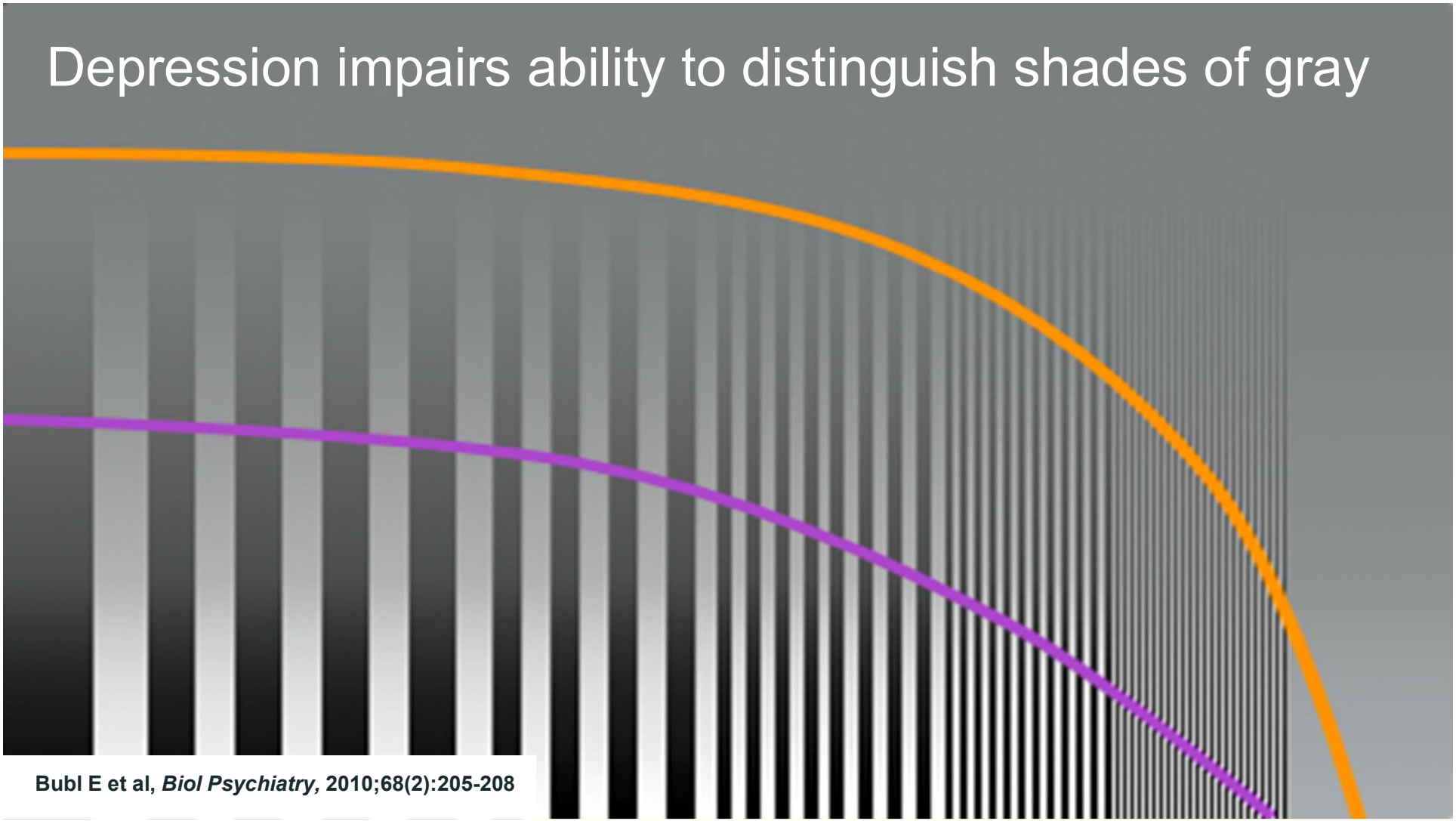
*Self-rated QIDS with algorithm-guided care based on QIDS level.
Both groups only allowed paroxetine and venlafaxine (n=120).

Guo T et al, *Am J Psych*, 2015;172:1004-13

Patient Report Doesn't Match Rating Scale



Depression impairs ability to distinguish shades of gray



Bubl E et al, *Biol Psychiatry,* 2010;68(2):205-208

Questions?

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